

### **REMARKS**

Claims 1 and 6-12 are currently pending in the application. Claims 1 and 6-12 are in independent form.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Amy E. Rinaldo, during a telephonic interview conducted on May 1, 2007. During the interview the cited prior art was discussed and no agreement was reached with regard to the patentability of the claims as pending.

The Office Action has held that the claims of the present application that recite sildenafil or statins are limited, with regard to priority, to the filing date of the present application. However, later in the Office Action the same claims are considered to be anticipated by the claims of US Patent No. 10,500,694 to which the present application claims priority. It is respectfully submitted that if the '694 patent is held to anticipate the presently pending claims, then the presently pending claims should be afforded the earlier filing date. Reconsideration of the priority is respectfully requested.

Claims 9-12 are objected to under 35 CFR 1.75 as being a substantial duplicate of claims 1, 6-8. In order to further prosecution, claim 9-12 have been cancelled without prejudice. Reconsideration of the rejection is respectfully requested.

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action has held that statins and phosphodiesterase inhibitors are not sufficiently described in the specification to provide sufficient examples for the genus of compounds. It is respectfully submitted that the specification as filed discloses that the compounds are capable of increasing nitric oxide and has indicated that known statins and phosphodiesterase inhibitors have the ability to increase nitric oxide as disclosed at page 5, lines 10-18 of the application as filed. Therefore, there is sufficient support

in the specification as filed for the compounds listed in the rejected claims. Reconsideration of the rejection is respectfully requested.

Claims 1 and 9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke et al. patent. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke et al. patent is respectfully requested.

The Office Action has held that the Cooke et al. patent teaches administering L-arginine in a vascular injury, with emphasis on atherogenesis. The Office Action has concluded that one of ordinary skill in the art would be motivated to administer L-arginine to patient, post stroke, in order to promote neurogenesis or growth of new neurons because L-arginine is the substrate for nitric oxide production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans. However, when read more specifically, the Cooke et al. patent merely discloses methods for limiting the occurrence or progression of atherosclerosis and restenosis or a method of increasing the blood flow to areas with decreased blood flow. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims. The method disclosed in the Cooke et al. patent has little to no applicability to the method recited in the presently pending independent claims.

In contradistinction, the presently pending independent claims claim therapeutic compounds including PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy is designed to be given days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after

stroke. The neurogenesis occurs as stated on page 7, lines 5-15 due to increased levels of cGMP resulting from the administration of the NO donor. The increased amount of cGMP increases the number of progenitor cells and the number of Tuj1 immunoreactive cells in the ischemic brain, thus enhancing the functional recovery after stroke. The recovery includes the increase of parenchymal cells as a result of the proliferation of new neurons, therefore, the parenchymal cells are increased as a result of the neurogenesis. cGMP functions to increase neurons. Additionally, the methodology disclosed in the Cooke et al. patent does not initiate neurogenesis. It is actually contrary to the common knowledge of those in skill in the art to have administered any compounds after the completion of the stroke. Instead, it was believed by those of skill in the art that upon completion of the stroke, an individual was no longer able to be treated and must instead learn to survive with the results of the stroke. Since the Cooke et al. patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Cooke et al. patent, and reconsideration of the rejection is respectfully requested.

Claims 1, 6-12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke et al. patent taken with the Liao patent in view of the Kaposzta et al. reference taken with the Ohtsuka et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke et al. patent taken with the Liao patent in view of the Kaposzta et al. reference taken with the Ohtsuka et al. reference is respectfully requested.

It is Hornbook Law that before two or more references may be combined to negative patentability of a claimed invention, at least one of the references must teach or suggest the benefits to be obtained by the combination. This statement of law was first set forth in the landmark case of Ex parte McCullom, 204 O.G. 1346; 1914 C.D. 70. This decision was rendered by Assistant Commissioner Newton upon appeal from the Examiner-in-Chief and dealt with the matter of combination of references. Since then many courts have over the years affirmed this doctrine.

The applicable law was more recently restated by the Court of Appeals for the Federal Circuit in the case of ACS Hospital Systems, Inc. v. Montefiore Hospital, 732

F.2d 1572,1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984). In this case the Court stated, on page 933, as follows:

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103 teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any such suggestion or incentive. Accordingly we hold that the court below erred as a matter of law in concluding that the claimed invention would have been obvious to one of ordinary skill in the art under section 103."

This Doctrine was even more recently reaffirmed by the CAFC in Ashland Oil, Inc. v. Delta Resins and Refractories, Inc., et al., 776 F.2d 281,297, 227 U.S.P.Q. 657,667. As stated, the District Court concluded:

"Obviousness, however, cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art which would have made such a combination appropriate."

The Court cited ACS Hospital Systems, Inc. in support of its ruling. This Doctrine was reaffirmed in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995).

As referenced above the Cooke et al. patent neither discloses nor suggests the invention as recited in the presently pending independent claims.

The Office Action has held that the Liao patent teaches a surprising connection was made in connection with the treatment of ischemic stroke, wherein brain injury reduction is measured by determining a reduction in the infarct size in treated versus control groups. At column 8, lines 62-65 there is further disclosed that the "brain injury reduction, as demonstrated in the examples below, can be measured by determining a reduction in infarct size in the treated versus the control groups." In other words, the treatment is similar to that of the Moskowitz patent previously cited in the present application, which does not provide the same results as accomplished by the method of the presently pending claims. As was found with regard to the Moskowitz patent, the Liao patent merely discloses that stroke can be

treated during a finite period of time. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. The Liao patent discloses at column 9, lines 21-30 that the treatment can either be prophylactic or can be acute. The acute treatment is defined as "at the onset of symptoms of the condition or at the onset of a substantial change in the symptoms of an existing condition." This definition is commensurate in scope with the knowledge of those of skill in the art defined above. Accordingly, there is no motivation for treatment after the stroke is complete, since this is a point in time substantially after the onset of the symptoms.

Finally, with regard to the Kaposta et al. and Ohtsuka et al. references, these references merely disclose use of compounds prophylactically. There is no disclosure for the use of the compounds post-stroke for creating neurogenesis. Since none of the cited references alone or in combination with one another suggest the currently claimed invention, it is respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not discussed above are ultimately dependent upon at least one of the independent claims discussed above. No prior art reference makes up for the deficiencies of that reference as applied against the independent claims as no prior art reference discloses or suggests the invention as set forth in the claims as discussed in detail above.

It is respectfully submitted that the present amendment places the application in condition for allowance as it removes all remaining issues in dispute. Specifically, the amendment follows suggestions set forth in the Office Action and clarifies the present invention. As a result, no remaining issues are in dispute. Since there is no prior art cited against any of these claims, it is respectfully submitted that all of the claims are in condition for allowance. It is also respectfully submitted that the present amendment places the application in condition for appeal. The claims have not been made broader in scope, thereby requiring no further searching nor raise

any new issues. In fact, all claims now include limitations of previously pending claims and were therefore previously searched.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. The claims have also been amended to clearly distinguish them over the prior art. The application is made at least in better condition for appeal as the amendment removes any issues thereby simplifying the issues on appeal. That is, each and every rejection has been overcome. Hence, it is respectfully requested that the amendment be entered.

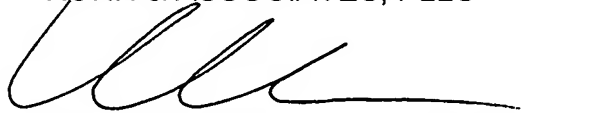
Applicants respectfully request to be contacted by telephone if any remaining issues exist.

In summary, the presently claimed invention is in condition for allowance, which allowance is respectfully requested. If any remaining issues exist, Applicants respectfully request to be contacted by telephone at (248) 539-5050.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES, PLLC



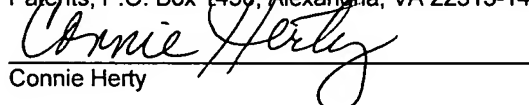
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CERTIFICATE OF MAILING

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